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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/689,366	ROTHE ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-28* is/are pending in the application.

4a) Of the above claim(s) *20,21,23,24,26 and 27* is/are withdrawn from consideration.

5)☒ Claim(s) *19* is/are allowed.

6)☒ Claim(s) *17,18,22 and 28* is/are rejected.

7)☒ Claim(s) *25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 8/4/03, in which the pending claims were cancelled and new claims were added (claims 17-28).

Response to Amendment

The amendment filed on 8/4/03 has been entered. Claims 17-19 essentially correspond to the elected invention and the claims that were under examination in the previous office action (i.e. claims 10-12). Claims 17 and 18 comprise additional functional limitations that exacerbate existing problems under 35 U.S.C. 112 1st paragraph. New grounds of rejection for the subject matter of claims 17-18 made herein were necessitated by applicants' amendment.

The subject matter of claim 19 has been found to be allowable. Applicants have previously requested rejoinder of all methods claims that incorporate all of the limitations of the subject matter of any allowed composition claims. Accordingly, claims 22, 25 and 28 have been rejoined for examination in this action. Thus, claims 17-19, 22, 25 and 28 are under consideration as the elected invention. Claims 20-21, 23-24 and 26-27 are withdrawn from consideration as being directed to nonelected inventions. As per MPEP 821.04, this action is FINAL.

MPEP 821.04 states in part:

> **In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action. (Examiner's emphasis added)**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new grounds of rejection necessitated by applicants' amendment filed 8/4/03.

Claims 17-18 are directed to isolated proteins comprising specific subsequences from c-IAP1 or c-IAP2 (described by SEQ ID NOS: 2 & 4, respectively). Claim 17 is directed to isolated proteins comprising the 3rd BIR domain of c-IAP1 (i.e. residues 287-334 of SEQ ID NO: 2 or SEQ ID NO: 9). Claim 18 is directed to a protein comprising at least two of 3 BIR domains chosen from combinations of the 3 BIR domains present in c-IAP1 or c-IAP2 (disclosed by applicants as SEQ ID NOS: 2 & 4, respectively). Claims 17 now comprises additional functional language that specifies that the BIR domain described by SEQ ID NO: 9 (claim 17) provides a protein:protein interaction domain which binds at least one of a specific pair of human tumor necrosis factor proteins (i.e. TRAF1 or TRAF2). Claim 18 now specifies that the entire protein comprising the different combinations of BIR sequences obtained from c-IAP1 and c-IAP2 binds at least one of a specific pair of human tumor necrosis factor proteins (i.e. TRAF1 or TRAF2). In the case of claim 17, there is no literal support in the specification for the functional limitation that the 3rd BIR domain of c-IAP1 alone provides a protein:protein interaction with TRAF1 or

TRAF2. Likewise, there is no literal support for the limitation that the full range of chimeric polypeptides encompassed by claim 18 possesses the specific functionality of binding to TRAF1 or TRAF2. Therefore, these newly added functional limitations are impermissible NEW MATTER.

These additional functional limitations mean that an even greater understanding of the structural/functional characteristics of the encompassed genus of proteins is required in order to envision those specific embodiments that retain functional activity. Claim 17 encompasses embodiments that do not possess all of the other BIR domains of c-IAP1 or c-IAP2, but which must retain the ability to interact with the TRAF proteins. Claim 18 encompasses a multitude of proteins comprising different combinations of the different BIR domains comprising different intervening sequences between domains that must retain the ability to interact with the recited TRAF proteins. The rejected claims further encompass embodiments where the human c-IAP protein comprises other functional domains in addition to the BIR and RING finger domains described in the art or in the instant specification and which must retain the recited functional activity.

The specification describes the isolation of cDNAs encoding c-IAP1 and c-IAP2 by probing human cDNA libraries with a nucleic acid encoding a murine version of c-IAP. The human c-IAP proteins are described as having significant similarity to the mouse version of c-IAP (84% and 72%, respectively, for c-IAP1 and c-IAP2) and 73% homology to one another. Unlike the insect viral analogs, the mammalian IAPs (c-IAP1 and c-IAP2) are described as comprising 3 BIR domains rather than two such domains. However, unlike NAIP, another mammalian apoptosis inhibitor, the instant proteins comprise a RING finger motif similar to

ones found in the insect viral analogs. Yeast two-hybrid analysis results are described which indicate that c-IAP1 and c-IAP2 interact with TRAF1 and TRAF2, two intracellular receptors for TNF. Deletion and hybrid experiments indicate that the BIR domains of c-IAP1 and c-IAP2 represent novel protein:protein interaction domains. The N-terminal domain of c-IAP1, comprising the 3 BIR motifs, is described as being sufficient to mediate interaction with the two receptors. The specification asserts that a hybrid protein comprising amino acid residues 46-99 and 204-249 of SEQ ID NO: 2 (c-IAP1) and 189-234 of SEQ ID NO: 4 (c-IAP2), separated by IAP1 derived intervening sequences of varying lengths "are assayed", but does not present any data concerning the ability of such hybrids to bind the TRAF proteins. The RING finger domain does not appear to be essential for c-IAP interaction with the TRAF receptors.

It is clear from the description provided by the specification that c-IAP1 and c-IAP2 share several similar structural/functional domains with one another and with different apoptosis inhibitors known in the art. For example, it is noted that the first BIR domains from each of c-IAP1 and c-IAP2 (described by SEQ ID NOS: 1 and 2) differ at only 1 amino acid residue out of a total of 55 residues. However, it is also evident from reading the specification that there are significant differences between the previously known inhibitors of apoptosis and c-IAP1/c-IAP2, as well as between c-IAP1 and c-IAP2 (e.g. 27% non-homology between the two proteins). There is no structural/functional framework provided in the specification to allow one of skill in the art to envision exactly what a 3rd c-IAP protein obtained from humans would look like. For example, would such a third c-IAP protein necessarily comprise a RING-finger domain? Would a 3rd c-IAP protein comprising SEQ ID NO: 5 or SEQ ID NO: 6 necessarily comprise other BIR domains similar to the ones described herein (e.g. SEQ ID NOS: 7-10)? The specification

teaches that it is the BIR domains that are likely to provide target specificity for c-IAP/target interaction. If additional human c-IAP proteins exist, it seems likely that they could be directed to other protein targets involved in mediating apoptosis. What would the BIR domains of such a protein look like? Again, the specification provides no basis to envision the primary amino acid sequence/structure of such a human c-IAP protein. Nor does the specification provide a basis for one of skill in the art to envision those specific embodiments, limited to comprising only the specific BIR domains obtained from c-IAP1 and c-IAP2 that would meet the functional limitations of the claims.

The prior art teaches that it is difficult to predict the structural/functional properties of a protein having a given primary amino acid sequence because the relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, the state of the art with regard to predicting the structural/functional characteristics of a protein having a given amino acid sequence is underdeveloped. Therefore, the prior art does not provide a structural/functional basis for one of skill in the art to envision additional embodiments of the claimed human c-IAP proteins comprising one or more of the recited domains of c-IAP1 and c-IAP2.

Given that the rejected claims encompass proteins comprising, or lacking, additional functional elements (e.g. BIR, RING-finger domains, different spacer sequences) to those described in the specification, and given that there is no structural/functional framework provided in the specification or prior art to envision additional embodiments of the claimed invention that meet the functional limitations of the claims, one of skill in the art would not have been able to envision a representative number of embodiments of the claimed c-IAP proteins to describe the genus of such proteins. Therefore, one of skill in the art would have reasonably concluded applicants were not in possession of the claimed invention.

Response to Arguments

Applicant's arguments filed in the amendment of 8/4/03 in response to similar grounds of rejection have been fully considered but they are not persuasive. The response essentially argues: 1) the amended claims expressly require the recited protein provide a protein:protein interaction domain that binds TRAF1 or TRAF2, 2) the specification teaches how multiple BIR domains can be mixed in different combinations to form functional chimeras, 3) the specification teaches how to identify functional chimeras, 4) discerning and practicing the claimed invention does not require invoking the legendary knights of King Arthur and does not relate to some hypothetical 3rd human c-IAP protein and 5) the invention is mundane and merely involves a novel protein:protein interaction.

While it is appreciated that applicants have attempted to limit the scope of those proteins encompassed by the rejected claims by reciting specific functional limitations, this has actually exacerbated the issues under 35 U.S.C. 112 1st paragraph regarding sufficient description of the proteins encompassed by the claims, for the reasons given above. With regard to assays for

determining those embodiments that interact with TRAF1 and/or TRAF2, these arguments are better suited to a rejection for lack of enablement, not rejections based on a lack of written description. As indicated previously by the examiner, the teachings of Berendsen (e.g. the "legendary knights of King Arthur") were supplied in order to demonstrate the unreliability of methods for envisioning the structural/functional characteristics of a given protein based upon primary sequence alone. An ability to do so would have aided the skilled artisan in determining those specific embodiments embraced by the rejected claims that retain the recited functional activity.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new grounds of rejection necessitated by applicants' amendment filed 8/4/03.**

Claim 22 is directed to a method of screening compounds that modulate human c-IAP interaction with a binding target based upon relative binding affinity of the c-IAP protein to the specific binding target in the presence and absence of the test compound. Claim 22 is limited to proteins that comprise SEQ ID NO: 2 (c-IAP1 as disclosed by applicants). A critical element of the invention is the specific binding partner for c-IAP1. The rejected claim, as currently written, encompasses any number of proteins that might reasonably be expected to bind in some fashion to c-IAP1 (e.g. specific caspase proteins).

The specification describes the isolation of cDNAs encoding c-IAP1 and c-IAP2 by probing human cDNA libraries with a nucleic acid encoding a murine version of c-IAP. The human c-IAP proteins are described as having significant similarity to the mouse version of c-IAP (84% and 72%, respectively, for c-IAP1 and c-IAP2) and 73% homology to one another. Unlike the insect viral analogs, the mammalian IAPs (c-IAP1 and c-IAP2) are described as comprising 3 BIR domains rather than two such domains. However, unlike NAIP, another mammalian apoptosis inhibitor, the instant proteins comprise a RING finger motif similar to ones found in the insect viral analogs. Yeast two-hybrid analysis results are described which indicate that c-IAP1 and c-IAP2 interact with TRAF1 and TRAF2, two intracellular receptors for TNF. Deletion and hybrid experiments indicate that the BIR domains of c-IAP1 and c-IAP2 represent novel protein:protein interaction domains. The N-terminal domain of c-IAP1, comprising the 3 BIR motifs, is described as being sufficient to mediate interaction with the two TRAF receptors. The specification asserts that a hybrid protein comprising amino acid residues 46-99 and 204-249 of SEQ ID NO: 2 (c-IAP1) and 189-234 of SEQ ID NO: 4 (c-IAP2), separated by IAP1 derived intervening sequences of varying lengths "are assayed", but does not present any data concerning the ability of such hybrids to bind the TRAF proteins. The RING finger domain does not appear to be essential for c-IAP interaction with the TRAF receptors.

It is clear from the description provided by the specification that c-IAP1 and c-IAP2 share several similar structural/functional domains with one another and with different apoptosis inhibitors known in the art. For example, it is noted that the first BIR domains from each of c-IAP1 and c-IAP2 (described by SEQ ID NOS: 1 and 2) differ at only 1 amino acid residue out of a total of 55 residues. However, it is also evident from reading the specification that there are

significant differences between the previously known inhibitors of apoptosis and c-IAP1/c-IAP2, as well as between c-IAP1 and c-IAP2 (e.g. 27% non-homology between the two proteins). The specification teaches that it is the BIR domains that are likely to provide target specificity for c-IAP/target interaction.

Proteins comprising the exact sequence recited in SEQ ID NO: 2 appear to have been novel in the art at the time of filing. Therefore the prior art does not provide a basis for one to envision other proteins that might interact with the c-IAP proteins encompassed by the rejected claims.

Given that c-IAP1 does share homology within its BIR domains to other apoptosis inhibitors known in the art, and given that there is no evidence that the functional activities of the other proteins are limited to, or even encompass TRAF1 or TRAF2, it is reasonable to expect that additional target proteins are encompassed by the rejected claims. The instant specification, however, provides no basis for determining what those additional targets might be for a protein comprising SEQ ID NO: 2. Therefore, the skilled artisan would necessarily have concluded that applicants were not in possession of the claimed invention.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new grounds of rejection necessitated by applicants' amendment filed 8/4/03.**

Claim 28 is directed to a method of inhibiting TNF-mediated apoptosis in a cell comprising the step of introducing into the cell a protein comprising SEQ ID NO: 2 whereby the protein promotes or inhibits TNF-mediated apoptosis in the cell and wherein the method is performed *in vitro*. There is no literal support in the specification as originally filed for this method. Specifically, there is no literal support for the step of introducing a protein comprising SEQ ID NO: 2 into a cell *in vitro*. While one may argue that one could introduce the protein into the cell via a nucleic acid encoding the protein, this does not provide support for a step that encompasses providing the isolated protein. Additionally, there does not appear to be support in the instant application as originally filed for the limitation of inhibiting TNF-mediated apoptosis in a cell *in vitro* by providing the isolated protein. Therefore, claim 28 is impermissible NEW MATTER.

Conclusion

Claims 17-28 are pending, with claims 17-19, 22, 25 and 28 under consideration. Claims 17-18, 22 and 28 are rejected. The subject matter of claims 22, 25 and 28 have been rejoined as the claims are limited to the subject matter of claim 19. Claim 19 is allowed. Claim 25 is objected to as being dependent upon a rejected claim, but would be allowable if rewritten in an independent form comprising each of the limitations of the claim upon which it currently depends.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Examiner
Art Unit 1636

ggl

GERRY LEFFERS
PRIMARY EXAMINER